

Diurnal Intraocular Pressure and the relationship with Swept-source OCT-derived anterior chamber dimensions in angle closure: The IMPACT Study.

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The corresponding author (R Bourne) confirms that he had full access to all the data in the study and has final responsibility for the decision to submit for publication.

Acknowledgments: Tomey Corporation (Nagoya, Japan) loaned the instrument for the purposes of the study.

Precis: Greater diurnal intraocular pressure fluctuation was associated with narrower swept-source OCT-measured anterior chamber angle dimensions in 40 individuals with either a primary angle closure or angle closure suspect diagnosis.

ABSTRACT

Purpose:

To evaluate diurnal intraocular pressure (DIOP) among individuals with Primary Angle Closure (PAC) or Primary Angle Closure Suspect (PACS). Additionally the hypothesis that greater DIOP fluctuation is related to smaller angle parameters was investigated.

Methods:

40 Caucasian newly referred untreated patients with bilateral PAC or PACS were recruited. Intraocular pressure (IOP) was measured hourly between 09.00 and 16.00 with Goldmann applanation tonometry. DIOP fluctuation was defined as difference between maximum and minimum IOP. Angle Opening Distance, AOD; Trabecular-Iris Angle (TIA); Angle Recess Area (ARA); Trabecular Iris Space Area (TISA) were measured with AS-OCT (CASIA) in dark (0.3-0.5 lux) and light (170-200 lux) on the same day as DIOP measurements in eight angle sections.

Results:

IOP declined as the day progressed ($p < 0.001$), unrelated to presence of PAS. At each timepoint, eyes with PAS ($n=31$) had significantly higher IOPs than eyes without PAS ($n=49$; $p=0.043$). DIOP fluctuation varied from 1.50 mmHg to 14.50 mmHg (mean 5.99 mmHg, SD 2.70 mmHg). DIOP fluctuation was unrelated to PAS.

Multiple-predictor models investigating association of angle dimensions and greater DIOP fluctuation were statistically significant for AOD 750 (light), ARA 750 (light and dark), TISA 500 (light), TISA 750 (light), TIA 500 (light) and TIA 750 (light and dark).

Conclusions:

DIOP variation has clinical implications given that IOP level is used to distinguish between diagnostic categories of PACS and PAC. OCT angle parameter measurements may predict for magnitude of IOP diurnal fluctuations in at-risk patients, which may be clinically useful when considering a clinical intervention.

INTRODUCTION

Raised IOP is an important risk factor for glaucoma, and it is the principal modifiable factor in the treatment of patients with and at risk of glaucoma. However, it is recognised that there is considerable variability of IOP during the day (diurnal fluctuation). IOP and the presence or absence of peripheral anterior synechiae (PAS) is used by clinicians to categorise a patient into differing diagnostic categories that reflect a differing risk for glaucoma categorised individuals as Primary Angle Closure Suspects (PACS) where only an occludable angle is present, and Primary Angle Closure (PAC), in which PAS and or a raised IOP are additionally observed, this latter diagnosis being accepted as a more advanced pre-glaucomatous state ¹.

Given the importance of the IOP level in this diagnostic classification, it is important to understand how representative a single IOP measurement taken in the seated position, is of the seated IOP profile throughout the day. The majority of studies that have investigated such 'diurnal variation' have been conducted in individuals with open anterior chamber angles ^{2,3}. Diurnal measurement of IOP, commonly termed 'phasing', is an important management tool when diagnosing or treating patients with diagnosed or suspected open angle glaucoma. PAS are areas of iridotrabecular contact. A histological study demonstrated that PAS are accompanied by adjacent damage to the trabecular meshwork ⁴. It is hypothesised that greater diurnal fluctuation would be observed in eyes with PAS than without.

New advances in Anterior Segment Ocular Coherence Tomography (AS-OCT) technology has made 3-dimensional (3D) swept-source OCT now possible. This technology based on the Fourier Domain technique gives the highest scanning resolution (11.6µm axial) for the angle space currently described ⁵. This higher

resolution gives a more precise identification of the position of the scleral spur and high intraclass coefficients of repeatability and reproducibility have been reported for this device, marginally higher than that for 2-dimensional AS-OCT ⁶. The substantial improvement in scan speed (30,000 A-scans per second) and the ability to image in 128 cross-sections are additional advantages of the swept-source OCT, which have enabled more precise and extensive measurements of angle structure.^{7, 8} The relationship between the degree of narrowing of an anterior chamber angle and the fluctuation of diurnal IOP (during office hours) has received minimal scientific attention ⁹. One may hypothesise that eyes with narrower anterior chamber angles would exhibit a greater diurnal IOP variation.

METHODS

Forty Caucasian consecutive patients newly referred to a hospital glaucoma service with a gonioscopic diagnosis (less than 180 degrees posterior pigmented trabecular meshwork visible on applanation gonioscopy) of bilateral Primary Angle Closure (PAC), Primary Angle Closure Suspect (PACS) or a combination of both conditions and no other ocular co-morbidity were recruited for the IMPACT study. The initial clinical examination and gonioscopy was performed by a single consultant ophthalmic surgeon with a specialist interest in glaucoma, specifically angle closure glaucoma (RB).

Diurnal Intraocular Pressure Measurement

Following recruitment to the study, participants attended for IOP measurement every hour from 9:00h to 16:00h, a total of 8 measurements (a time window of +/- 15 minutes around each clock hour was permitted). Measurements involved Goldmann tonometry (Goldman Tonometer HS Haag-Street International AT900, Koeniz, Switzerland) using disposable prisms to reduce the risk of cross-contamination. The same tonometer was used for every IOP measurement for every participant and regular calibration checks were undertaken, with no calibration errors detected during the study. Two IOP measurements were taken per eye with a maximum of 1 mmHg difference permitted between these measurements.

Image Acquisition

Three-dimensional AS-OCT (Casia device, Tomey, Japan) images were obtained on the same day as the IOP measurements. The scans were taken in darkness (between 0.3 and 0.5 lux) and in light conditions (between 170 and 199 lux) and the images taken were subsequently analysed using the commercially available software

with this instrument. Acquisition and analysis of images was undertaken by the same examiner (LSP) throughout.

Image Analysis

The analysis of AS-OCT images acquired in dark and light conditions involved calculation of the following parameters in each eye (Figure 1): the angle opening distance (AOD), the trabecular-iris angle (TIA), ¹⁰ the angle recess area (ARA) ¹¹ and the trabecular iris space area (TISA).¹²

These parameters were quantified in eight sections of the angle (Superior, Superior-Nasal, Nasal, Inferior-Nasal, Inferior, Inferior-Temporal, Temporal and Superior-Temporal) and at 500 and 750µm from the scleral spur (Figure 2).

Right and left eyes of 35 participants were included in the analysis. Five out of a total of 40 participants in the study were imaged with a different AS-OCT device at the beginning of the study therefore their results were excluded for this analysis.

Statistical analysis

A participant's DIOP peak was defined as the highest pressure in either eye during this time period. Using both single-predictor and multiple-predictor regression models, diurnal IOP fluctuation was related to each angle section in both light and dark conditions. Single predictor variables included gender, age, presence of PAS (any observable PAS as assessed with applanation gonioscopy), and extent of PAS (circumferential angle degrees over which PAS extend).

Ethical approval by Cambridgeshire Research Ethics Committee (REC) for the Investigating Management of Angle Closure and Treatment (IMPACT) study was

obtained on the 3rd August 2010 (REC Reference 10/H0301/14). The study was entered on the National Institute for Health Research Clinical Research Network (NIHR CRN) Portfolio on 9th September 2010. NIHR CRN Study ID: 8955. The research adhered to the tenets of the Declaration of Helsinki.

RESULTS

Of the 40 participants recruited, 27 were female and 13 were male. The average age in the group was 59.6 years at the time of recruitment (range 25-77 years).

All were Caucasian. At the time of recruitment, 23 participants were diagnosed with bilateral PAC, 14 with bilateral PACS and 3 with a combination of both conditions.

Diurnal Intraocular Pressure (DIOP)

The mean IOP at each timepoint for 80 eyes of the 40 participants is presented in Figure 3. The highest mean IOP was found to be at 09:00 hours (18.5 mmHg; SD: 4.27 mmHg; Range: 12.0- 30.5 mmHg).

The maximal diurnal IOP was found to be at 09:00h for 28 participants, at 10:00h for 5 participants, at 11:00h for 4, at 13:00h for 1, at 14:00h for 3 and at 15:00h for 1 participant.

Effect of the presence of Peripheral Anterior Synechiae (PAS) on Diurnal Intraocular Pressure (DIOP) measurements

A repeated measures analysis of variance showed a statistically significant decline in IOP as the day progressed ($p < 0.001$), which was not related to whether or not PAS were present. There was no statistically significant interaction between presence or absence of PAS and time of measurement ($p = 0.458$).

However, at each timepoint, eyes with PAS ($n = 31$) had statistically significantly higher IOPs than eyes without PAS ($n = 49$). An average of difference between means was found to be 1.5 mmHg higher for those eyes with PAS ($p = 0.043$). This effect was not related to the time of measurement.

DIOP and the circumference of PAS (measured in degrees) showed a statistically significant positive relationship ($p < 0.05$, calculated using single-predictor regression), at each timepoint. These models showed a similar relationship between the response variable (IOP at different times-DIOP) and the predictor variable (degree of PAS), which were all statistically significant except for the measurement taken at 12:00h ($p = 0.08$).

Diurnal Intraocular Pressure Fluctuation (DIOP Fluctuation) and the presence of Peripheral Anterior Synechiae (PAS)

The average fluctuation in DIOP was defined as the difference between the average for the maximum value of IOP attained during the DIOP (mean maximal IOP, 20.03 mmHg; SD 4.18) and the minimum for a given eye (mean minimal IOP, 14.04 mmHg; 2.82). The mean fluctuation for this sample of eyes was found to be 5.99 mmHg (2.70 SD) and diurnal fluctuation of IOP ranged from 1.50 mmHg to 14.50 mmHg within the group.

Regression models were fitted in order to investigate any relationships between the response variable DIOP fluctuation and the predictors age, gender, presence/absence of PAS and circumferential degrees of PAS (Table 1). No relationships were found between range of fluctuation of DIOP and the single predictors age, gender, presence/absence of PAS, or circumferential degrees of PAS. This model was adjusted for gender and age to be able to enable comparison with the results of Baskaran et al ⁹.

Table 1. Single-predictor and multiple-predictor regression models of DIOP fluctuation with age, gender, presence/absence of PAS and degree of PAS adjusted.

	Single-predictor Regression Analysis			Multiple-predictor Regression Analysis		
	Standardized Coefficients	P value	Adj. R ²	Standardized Coefficients	P value	Adj. R ²
Gender	-0.061	0.590	- 0.009	-0.043	0.705	- 0.014
Age	0.114	0.316	0.000	0.150	0.242	
Presence/Absence of PAS	-0.055	0.625	- 0.010	-0.178	0.251	
Extent of PAS	0.045	0.691	- 0.011	0.182	0.242	

Relationship between diurnal IOP fluctuation and anterior chamber dimensions

The higher contribution to the model was achieved by negative regression coefficients showing an inverse relationship between magnitude of IOP fluctuation and angle dimensions. In the case of the single-predictor models almost all the coefficients were negative (97%; 124 of 128 single-predictor models; Figure 4). The multiple-predictor models (Table 2) were statistically significant ($p < 0.05$) for AOD 750 (light), ARA 750 (light and dark), TISA 500 (light), TISA 750 (light), TIA 500 (light) and TIA 750 (light and dark).

Table 2. Single-predictor and multiple-predictor regression models of DIOP

fluctuation for light and dark conditions with angle parameters adjusted for the eight angle sections. Sections in which there was a statistically significant relationship in the single-predictor model are given, in addition to the results of the multiple-predictor model.

Angle parameter	LIGHT			DARK		
	single predictor model Sectors with significant relationship	multiple predictor model Adjusted R ²	multiple predictor model P-value	single predictor model Sectors with significant relationship	multiple predictor model Adjusted R ²	multiple predictor model P-value
AOD500	S, S-N, I-N, I, T	10.1%	0.094	S-N, I-N	7.4%	0.141
AOD750	S, S-N, I-N, I, T	24.9%	0.002*	S, S-N, I-N	7.3%	0.145
ARA500	S, S-N	13.1%	0.052	S-N, I-N	9.7%	0.091
ARA750	S, S-N, I-N	18.9%	0.012*	S, S-N, I-N	16.1%	0.023*
TISA500	S, S-N, I-N	16.4%	0.029*	S-N, I-N	9.3%	0.098
TISA750	S, S-N, I-N, I, T	25.3%	0.002*	S, S-N, I-N, I	10.0%	0.086
TIA500	S, S-N, I-N, I, T	18.5%	0.012*	S-N, I-N, I	7.9%	0.126
TIA750	S, S-N, I-N, I, T	25.3%	0.002*	S-N, I-N	17.3%	0.016*

S = Superior, N = Nasal, I = Inferior, T = Temporal, S-N = Superior-Nasal, S-T = Superior-Temporal, I-N = Inferior-Nasal, I-T = Inferior-Temporal.

DISCUSSION

The dynamic balance between aqueous production and outflow leads to IOP fluctuation in healthy and glaucomatous eyes. The pattern of IOP fluctuation can be highly variable and sensitive to the effects of body posture, hydration, and aging. Maximal IOP in this study was measured in the morning (9:00 to 11:30h) for the majority of participants. Wilensky observed that 65% of normal subjects (defined as subjects with normal IOPs, normal visual acuity, healthy optic nerve heads and no history of ocular disease) had diurnal IOP peaks between 08:00 and 14:00h while 30% exhibited a peak IOP between 04:00 and 08:00.² Differing results were reported for those diagnosed as ocular hypertensive (IOP >22mmHg and no signs of glaucoma) where 51% presented their peaks between 04:00 and 08:00 and 42% between 08:00 and 14:00. In the case of the present study, if an equivalent IOP based criterion to that in the study by Wilensky is used ² (22mmHg or less) and the presence of PAS is ignored, 28 of 40 participants (70%) had IOP ≤ 22mmHg in both eyes during the diurnal period. Of these 28 participants, 27 (96%) exhibited an IOP peak between 09:00 and 14:00h. Of the participants with IOP >22mmHg in at least one eye (n=12), all had a peak IOP that occurred between 09:00h and 11:00h. To summarize, in both this study and that of Wilensky ², diurnal peaks are more frequently found in the morning than in the late afternoon (after 14:00h) and this was unrelated to a particular IOP cut off.

The DIOP pattern found for this group of subjects is similar to that in a study of 21 healthy individuals in a similar age group and mixed ethnicity (15 of 21 subjects were Caucasian) by Liu et al.³ In that study, Liu et al reported a peak in the early morning of approximately 18mmHg, a decrease throughout the morning to levels of 17mmHg, with a moderate increase in the middle of the day (12:00h) of approximately 0.5

mmHg, decreasing further to levels of 17 mmHg in the early evening (16:00h). This is therefore an interesting observation that, despite the fact that the participants in the present study had narrow angles and higher DIOP fluctuation, the DIOP behaviour was similar to that reported for patients with open angles in other studies.

Of 80 eyes of 40 patients examined at Visit 1, 49 were diagnosed as PAC and 31 as PACS. From those eyes diagnosed as PAC, 17 were due to presence of PAS only and 18 were due a raised IOP only (IOP higher or equal to 21mmHg at any time between 9:00 and 16:00 hours) and 14 were due to a combination of PAS and IOP criteria. Of the 18 eyes diagnosed with PAC due to IOP levels only, 15 would have been diagnosed as PACS had the IOP measurements been taken in the afternoon (12:30h to 16:00h). This highlights the observation that the timing of a single IOP measurement by a clinician is of importance when considering which diagnosis to ascribe a patient with angle closure. In this case, 6 participants might be ascribed the lower risk PACS diagnosis, had the single afternoon IOP measurement been the only measure used to reach a diagnosis. This may be of clinical importance given that the management and follow-up of patients diagnosed as PAC differs from those diagnosed as PACS.

To date there are no studies published that report the relationship of diurnal IOP with PAS. The present study found a statistically significant effect of the presence of PAS on DIOP. The IOP of an eye with PAS was on average 1.5 mmHg higher than in an eye without PAS. Furthermore, the increase in IOP was found to be directly related to the degree of PAS present in an eye at the majority of the diurnal timepoints.

Few studies have reported diurnal fluctuation of IOP for normal (non-glaucomatous) and glaucomatous eyes.^{9, 13, 14} A literature search failed to identify studies

investigating diurnal IOP fluctuation among untreated individuals with angle closure in the absence of glaucoma. In a study of Chinese patients whose eyes had previously been treated with LPI with a diagnosis of PAC or PACG, Baskaran et al reported higher levels of fluctuations in these patients (fluctuation defined as the difference between peaks and troughs of diurnal intraocular pressure).⁹ In that study, PAC and PACG patients presented with greater diurnal fluctuation of 5.4 ± 2.4 and 4.5 ± 2.3 mmHg, respectively (IOP measured every hour from 8:30 to 16:30h) compared to those with PACS and normal subjects with open angles, 3.7 ± 1.2 and 3.8 ± 1.1 mmHg, respectively. The same study reported a relationship between the diurnal fluctuation of IOP in the same eye and the degree of PAS of these patients. These findings differ from our study in which fluctuation of DIOP was not related to age, gender or PAS. In the case of the present study the lack of a relationship is not unexpected given that the DIOP patterns of those eyes with presence of PAS and those eyes without were very similar (Figure 5). Although there may have been differences between the peaks and troughs between patterns, the fluctuation obtained would have been similar. In the study by Baskaran et al, the data showed a high degree of variation and, although the relationship was reported as statistically significant ($p = 0.013$), the relationship was weak (R^2 , 0.139).⁹

Diurnal IOP fluctuation and anterior chamber dimensions

The results found for diurnal IOP fluctuation suggested that an eye with smaller angle dimensions would exhibit a greater range of IOP (difference between peak and trough) during the day. Furthermore, the multiple-predictor statistical models were able to predict this fluctuation from OCT measurements of anterior chamber angle parameters. This is a novel finding. Were this to be confirmed with a larger sample

size, it is possible that OCT angle parameter measurements could be used to predict IOP diurnal fluctuations in at-risk patients, allowing clinicians to selectively offer laser treatment to those where a higher diurnal IOP range would be judged as high-risk.

No allowance in our analysis was made for the correlations between eyes of the same individual, which is the case with many similar studies in this field, and some may consider this a limitation of this study.

The enhanced scan speed, clarity of visualisation of the scleral spur and ability to take measurements of more than a hundred cross-sections of the anterior chamber angle that is possible with swept-source OCT, lends advantage to using this technology as compared to conventional AS-OCT.

Conclusion

Clinicians should be aware of changes in IOP that occur throughout the day in patients with occludable anterior chamber angles and that higher IOP levels during the day is related to the circumferential extent of PAS compared to normals. In clinical centres where laser peripheral iridotomy is only applied to those individuals with a more advanced pre-glaucomatous stage (PAC), the present findings would support measuring IOP in the early morning to establish the maximal IOP.

Acknowledgments

The authors wish to acknowledge the staff of the Department of Ophthalmology at Hinchingbrooke Hospital, Huntingdon, UK, who hosted the study, in particular Paula Turnbull, Heather Pearman and Jane Kean who provided administrative and clinical support for the study. Sancy Low is also thanked for her participation in discussions

on anterior chamber angle image analysis. This study was supported by an Anglia Ruskin University student grant and a research grant from Allergan Ltd.

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FIGURES

Figure 1. Irido-trabecular angle parameters as measured with the CASIA AS-OCT analysis software. AOD (Angle Opening Distance), ARA (angle Recess Area), TISA (Trabecular-Iris Space Area) and TIA (Trabecular-Iris Angle) at 500 and 750µm are highlighted in bright green colour.

Figure 2. Schematic explanation of the eight irido-trabecular angle sections under study (please note that these are corresponding to the right eye). The abbreviations found in this figure are those corresponding to the sections and position-degree in the ocular circumference. Abbreviations: S=Superior (90 degrees), S-N=Superior-Nasal (45 degrees), N=Nasal (0 degrees), I-N= Inferior-Nasal (315 degrees), I=Inferior (270 degrees), I-T=Interior-Temporal (225 degrees), T=Temporal (180 degrees), S-T=Superior-Temporal (135 degrees).

Figure 3. Mean (and standard deviation) Intraocular Pressure at hourly timepoints (80 eyes of 40 participants).

Figure 4. Histograms of standardised regression coefficients for 128 single-predictor regression models of DIOP fluctuation for light and dark conditions with angle parameters adjusted for the eight angle sections.

Figure 5. Mean (and standard deviation) Intraocular Pressure at hourly timepoints in eyes with PAS (n=31) and without PAS (n=49).